





# Arsenic in Drinking Water: Cessation Lag Model

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## **I. Cessation Lag Estimation: Introduction**

In the risk analysis for its January, 2001 rule for arsenic (As), EPA considered that there was a latency period after exposure, time period between initial exposure to As and cancer mortality, in its benefits calculations. Defining such a latency period is highly uncertain. It is likely that latency depends on both the tumor type and site as well as the causes of the cancer. The factors involved in latency are poorly understood by health scientists. The Agency recognizes, however, that despite significant uncertainty in the latency period associated with As exposure through drinking water, it is unlikely that all cancer reduction benefits would be realized immediately upon exposure reduction. To the extent that there are delays due to latency in the realization of these benefits, monetized cancer reductions benefits would need to be discounted. It is also apparent that one cannot consider the delays due to latency without also considering the immediate benefits reaped from the initial reduction in exposure. The Science Advisory Board (SAB) used the term “cessation lag” to define that period between initial reduction in exposure to achievement of steady state benefits reduction at that lower exposure level. In *The Arsenic Rule Benefits Analysis: An SAB Review* (USEPA, 2001), the SAB panel recommended that EPA estimate cessation-lag but did not provide additional information or suggested approaches to quantify estimates for either cancer or noncancer endpoints associated with human exposure to arsenic.

Because additional information on how to calculate a cessation lag was not provided, EPA reviewed the epidemiological literature for information relating to the timing of exposure and response (Brown and Chu, 1983; Hazelton et al., 2001; Borgono et al., 1977 and Chiou et al., 2000); there were no studies to support a specific cessation lag estimation for As in drinking water. In the absence of arsenic data, EPA chose to model the potential cessation lag based on smoking cessation data. The literature on smoking cessation is by far the most complete body of information on this subject. The data for smoking cessation data cover lung cancer and heart disease, two endpoints associated with exposure to arsenic in drinking water. Also, the smoking cessation cohorts studied are large which reduces statistical uncertainty in the analysis.

There are, however, uncertainties associated with using the smoking cessation data in lieu of arsenic-specific information; and thus, a number of assumptions have to be made for adequate interpretation. A key assumption is in the comparison of the modes of action for Arsenic to that of tobacco smoke.

### ***The Potential Mode(s) of Action for Arsenic (As)***

Both high and low dose exposures of humans to various forms of As have been associated with a wide array of adverse effects ranging from death to cancers to dermal lesions (NRC, 1999, 2001). There are several examples of acute human high dose exposures. Instances include the use of Lewisite, an arsenical war gas (Peters et al., 1945), high dose exposures to As in beer (Kelynack et al., 1900), powdered milk (Hamamoto, 1955) or soy sauce (Mizuta et al., 1956). Such exposures have been reported to lead to death and severe hematological, neural and gastrointestinal effects. On the other hand, chronic low dose exposures to As have been reported

to cause various internal cancers and skin cancer, cardiovascular, dermal and neurological effects (NRC, 1999, 2001; Chappell et al., 2001). Since the US EPA is primarily concerned with the effects of low-dose environmental exposures, this discussion will consider some of the possible mode(s) of action (MoA) of the carcinogenic effects of chronic low-dose exposures.

Cancers and non-cancer diseases are generally considered as separate types of effects. For non-carcinogens, it is believed that a certain level of exposure is necessary - a so-called "threshold"- for a disease to occur. On the other hand, for cancer induction, the EPA accepts the theory that it is possible for one molecule of a chemical to react with a cell's DNA and cause a cancer to develop. Arsenic is unusual among the carcinogenic chemicals regulated by EPA for two major reasons: (1) the As risk assessment is based on human populations exposed to As in drinking water; and (2) there is no accepted animal model for As-induced carcinogenesis (NRC, 1999). Accordingly, most of the data on possible MoAs will come from *in vitro* studies.

Whether humans are exposed to the pentavalent ( $\text{As}^{+5}$ ; arsenate) or trivalent ( $\text{As}^{+3}$ ; arsenite) forms of inorganic arsenic in drinking water, As is sequentially methylated to form monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). Although the complete metabolic schema is not known, most of the reactions are known. The pentavalent form of inorganic As (if present) is reduced to the trivalent species. This form is methylated to make  $\text{MMA}^{+5}$ . The  $\text{MMA}^{+5}$  is then reduced to  $\text{MMA}^{+3}$  and methylated to  $\text{DMA}^{+5}$ . The  $\text{DMA}^{+5}$  can be reduced to  $\text{DMA}^{+3}$  but this form does not appear to be methylated in humans (NRC, 2001).

Originally, it was thought that  $\text{As}^{+3}$  was the putative toxic form of inorganic As due to its ability to inhibit over 200 enzymes (Webb, 1966) and that it was more potent than  $\text{As}^{+5}$  in blocking metabolic pathways (Szincz and Forth, 1988). The tri- and pentavalent forms of MMA and DMA could not be separated and identified; the limited toxicity testing of MMA and DMA revealed that they were less potent than arsenite or arsenate. (It is now known that the MMA and DMA species tested were more stable than the pentavalent forms.) Therefore, it was proposed that methylation was a detoxification pathway (Marcus and Rispin, 1988). Recently, it has been reported that both the trivalent and pentavalent forms of monomethylarsonic (MMA) and dimethylarsonic (DMA) acids are excreted in the urine (Aposhian et al., 2000; Mandal et al., 2001). This is important as it was previously believed that only the pentavalent forms of MMA and DMA were sufficiently stable to be excreted in the urine. Work by Styblo et al. (2000) and Petrick et al. (2000) has shown that  $\text{MMA}^{+3}$  and  $\text{DMA}^{+3}$  are generally more potent enzyme inhibitors than  $\text{As}^{+3}$  and are more toxic to some tested cell lines than the trivalent form of inorganic As and in some assays,  $\text{MMA}^{+3}$  is the most active form. This is relevant as humans excrete more total MMA (includes both the tri- and pentavalent species) than do experimental animals. Another potentially important factor is that there is variation in the metabolism of As among human individuals and populations (Concha et al., 1998, Vahter, 2000). Thus, the toxicity of As may be related not only to the valence states, but also to the relative proportions of the trivalent and pentavalent As species produced by an individual. The above data on the toxicity of the trivalent methylated metabolites of As to cells and on enzymes in *in vitro* systems (Styblo et al., 2000; Petrick et al., 2000) indicate that methylation may not be a detoxification pathway.

Arsenic has many effects on the cell, but there is no generally accepted MoA for As-induced carcinogenesis. Although it had been previously tested many times, inorganic As had not been reported to react with DNA. Mass et al. (2001) examined the possibility that some of the various forms of As, including the trivalent MMA and DMA, reacted directly with DNA. They found that  $\text{MMA}^{+3}$  (30 mM) and  $\text{DMA}^{+3}$  (150  $\mu\text{M}$ ) could “nick” the DNA, while Arsenite (+3) had no effect in this system. In addition,  $\text{MMA}^{+3}$  and  $\text{DMA}^{+3}$  were 77 and 386 times more potent than arsenite in causing DNA damage in human lymphocytes. These results demonstrate that under experimental conditions  $\text{MMA}^{+3}$  and  $\text{DMA}^{+3}$  can directly interact with DNA, but at higher concentrations.

There are other possible MoAs for As. Several reports have shown that arsenic can affect DNA indirectly. For example, arsenite induced formation of micronuclei in human fibroblasts (Yih and Lee, 1999). Since this action was blocked by catalase and N-acetyl cysteine, the authors suggested that the micronuclei might have been caused by oxidative stress. It is of interest and relevant that micronuclei have been reported in the exfoliated bladder cells of humans exposed to As in drinking water (Moore et al., 1997). *In vitro* experiments have shown that arsenite can cause increases in superoxide and  $\text{H}_2\text{O}_2$  (Barchowsky et al., 1999), cause formation of iron-dependent reactive oxygen species (Ahmad et al., 2000), induce heme oxygenase (Kitchen et al., 1999) and inhibit thioredoxin reductase (Lin et al., 2001). These reports demonstrate that As exposure can affect oxygen free radical formation which could damage DNA (NRC, 1999; 2001).

Liou et al. (1999) found a higher frequency of chromosome gaps, breaks and breaks plus exchanges in Taiwan people exposed to As. Possibly related to these human effects is the data that 1  $\mu\text{M}$  arsenite can DNA-protein cross-link in human liver cell lines (Ramirez et al., 2000). The authors suggest that this effect could play a role in the formation of chromosome aberrations observed after exposure to As.

Arsenic also has been reported to have many other effects that could play a role in the development of cancer(s). It can increase DNA synthesis, affect protein kinases and p53 proteins. Such results show that arsenic can also affect pathways that are implicated in the promotion and progression of tumors (NRC, 1999; 2001). There is additional evidence that arsenite can be co-mutagenic with UV light (Rossman, 1981). The exact role this effect would play, e.g., promotion, progression or co-carcinogen, in the development of cancer(s) is uncertain at the present time. Moreover, arsenic can also inhibit DNA repair (Snow, 1999), methylation of CpG sites in DNA (Zhong and Mass, 2001) and alter nuclear binding of some transcription factors (Kaltreider et al., 1999). These reports demonstrate that As can affect gene expression (NRC, 1999; 2001). With the plethora of effects caused by As exposure, there is no agreement on one MoA for As (NRC, 2001) and at the present time, it is not possible to select one MoA as the most likely. In the language of the EPA proposed revisions to the Guidelines for Cancer Risk Assessment (U.S. EPA 1999) there has been no demonstration of critical steps of an arsenic mode of action. An additional consideration is that the effects of  $\text{MMA}^{+3}$  and  $\text{DMA}^{+3}$  have not been tested in many of these experimental systems. It is possible that once the trivalent methylated metabolites of arsenic are tested, a clearer picture of the carcinogenic action of As will emerge. It can be said that arsenic compounds can damage DNA directly, alter DNA indirectly and/or act as

an initiator/promoter/progressor/co-carcinogen. Due to the lack of arsenic-specific cessation lag data and the uncertainty surrounding the MoA for As, it was decided to use the data on smoking to develop a cessation lag model.

### *The Modes of Action for Tobacco Smoke*

Both the SAB and the Peer Reviewers addressed the importance of considering the mode of action of a carcinogen to inform the development, use and interpretation of the cessation lag model. Both SAB and the Peer Reviewers observed that if As (or any carcinogen) acts primarily as a late-stage carcinogen (promoter) the time period to attain lower levels of risk following cessation or reduction in exposure is expected to be much shorter than it would be if As acts primarily as an early-stage carcinogen (initiator).

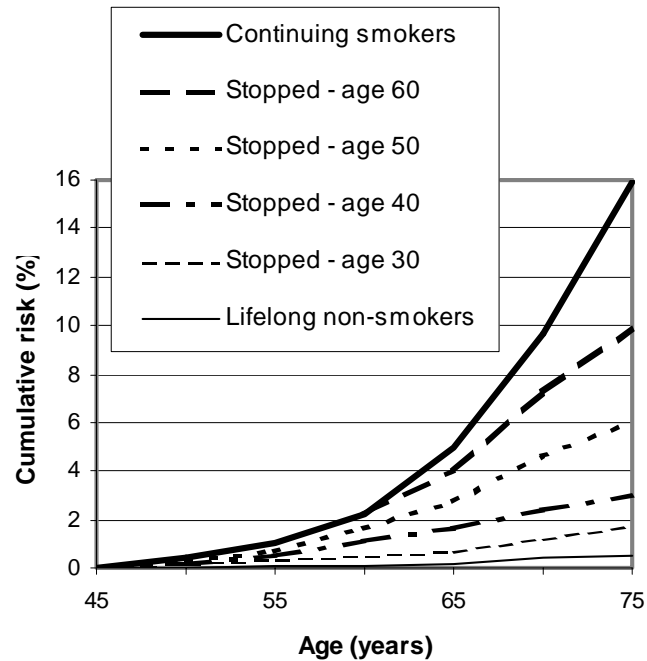
The available information on the carcinogenic mode of action of As is not conclusive, with some data suggesting it has a predominately promoting effect and other data indicating a mixture of initiating and promoting effects. To aid in the use of smoking cessation data as a surrogate model for assessing the risk reductions from reducing or eliminating exposure to As, it is also important to understand the initiation-promotion aspects of cancer caused by tobacco smoke. The available data on the carcinogenicity of tobacco smoke is also mixed in this regard.

Wang and Samet (1997) note that while tobacco smoke is known to contain a number of carcinogens, the specific mechanisms by which most components of tobacco smoke cause cancer have not yet been characterized. Williams et al. (2000) note that research has identified more than 40 carcinogenic substances emitted in tobacco smoke and that many of these are genotoxic initiating agents capable of inducing cancer by themselves, while others are recognized as being promoters or co-carcinogens. The NAS (2001) states that use of tobacco products results in exposure to more than 100 mutagens and carcinogens. NAS (2001) also notes that current data do not exist to indicate what stage in the process of tumor development is preferentially affected by tobacco constituents but that an effect on all stages is plausible and suggested by the complex genetic alterations observed in lung and other cancers.

As such, it would be expected that the effect of smoking cessation on cancer incidence would reflect some combination or blending of the expected pattern from substances that are either primarily initiators and those that are primarily promoters.

Exhibit 1 below from Peto et al. (2000) provides some indication of this mixed behavior. If the carcinogenic action of tobacco smoke were predominately that of a promoter, then the risk for those subgroups that stop smoking at any indicated age would be expected to remain relatively level at the cumulative risk value associated with the time when quitting occurred, and possibly even falling to a level closer to that of the life-long non-smokers. On the other hand, if the carcinogenic action of tobacco smoke were predominately that of an initiator, then the risk for those subgroups that stop smoking at any indicated age would be expected to show a pattern of continued increase in cumulative lifetime risk more similar to (though less than) that of the continuing smokers. The Peto et al. (2000) data shown in Exhibit 1 suggest the expected mixed

pattern with indications of both initiation and promotion behavior. For individuals that quit at a relatively early age, the cumulative risks do tend to level off as would be expected for substances having primarily a promoting effect, but still continue to increase for the remaining lifetime at a rate somewhat higher than that for non-smokers. For those stopping at a relatively later period, the cumulative risks continue to rise in a pattern more similar to that of the continuing smokers, as would be expected for substances having primarily an initiating effect, although the risk appears to be starting to level off for those quitting at age 50.



**Exhibit 1. Smoking cessation effects at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at 1990 death rates for U.K. men (Non-smoker risks taken from a US prospective study of mortality) Adapted from Peto, et. al. 2000.**

The smoking cessation lag model developed in Section I.3, below, from the Hrubec and

McLaughlin (1997) data has the form:

$$RR = B * (\text{years of cessation})^{-0.77}$$

where B is the risk at the time of cessation and for the first year afterwards. B depends on a person's smoking level before cessation.

As discussed in this document, the model and the underlying data suggest a very rapid decrease in risk after smoking cessation such that 41.4% of the maximum achievable risk reduction occurs in the first year and an additional 15.7% in the second year following cessation. Almost 71% of maximum achievable reduction occurs in the first five years following cessation. This pattern of risk reduction is somewhat more suggestive of tobacco smoke exhibiting a promoter mode of action than an initiator mode of action.

There is clearly some measure of uncertainty inherent in the application of the smoking cessation lag model developed by EPA for As. That both tobacco smoke and As appear to exhibit a combination of both initiator and promoter modes of action lends support to using the smoking cessation model as a surrogate for evaluating the risk reduction benefits of reducing exposure to As. At the same time, it is recognized that the specific form of the smoking cessation lag model appears to emphasize promoter behavior more than initiator behavior. If As also operates primarily as a promoter (as some studies suggest), then the smoking cessation lag model as currently developed would arguably be a reasonable model for As as well. If, however, the As mode of action is more of a mixture of initiator and promoter than the current smoking cessation lag model reflects, then it may be overestimating the rate of risk reduction from reducing exposure to As.

The general approach for use of smoking cessation data will be the development of statistical models for lung cancer and coronary heart disease and then to overlay these risk reduction models on the disease mortality and incidence calculations for As cancer and noncancer endpoints. The assessment will assume that the specific cessation-lag for lung cancer due to smoking approximates that for all cancers associated with ingested As exposure. Likewise, the specific coronary heart disease cessation-lag for smoking is assumed to approximate that for all noncancer endpoints attributable to ingested-As. These assumptions are supported by the toxicologic information available for ingested As which suggests that all cancer endpoints may be related mechanistically. Similar mechanistic arguments can also be made that all noncancer endpoints are related.

## I.1. Studies of Cancer

### 1. *Hrubec and McLaughlin (1997)*

Hrubec and McLaughlin (1997) is the most appropriate study for development of a statistical model of disease response to smoking cessation for both lung cancer and coronary heart disease. This study, which is the most recent followup of almost 300,000 U.S. veterans, began in the 1950s. By the time of this evaluation, 198,172 deaths were already recorded. Almost all were white males. Mortality was ascertained using the Veterans Administration's beneficiary ID and records locator system. The causes of death were determined by trained nosologists. A cause of death was coded for 97% of deaths. Data were computed using internal standardized relative risks (RRs), standardized mortality rates (SMRs), and standardized annual mortality rates (SAMRs). RRs and SMRs were calculated for all former smokers, as well as those who had stopped smoking for <5, 5-9, 10-19, 20-29, and 30-39 years. Additionally, for each duration since cessation of smoking, the cohort was further divided into groups who had previously smoked 1-9, 10-20, 21-39, and 40+ cigarettes/day. SMRs and RRs were derived for these groups for durations since cessation of smoking listed above. A summary of lung cancer and coronary heart disease relative risks are shown in Tables I-1 and I-2. The breakdown by number of cigarettes is shown to illustrate that the relative magnitude of the risk reduction is fairly independent of this variable.

**Table I-1. U.S. veteran males: relative risks lung cancer based on comparison of never smokers (RR = 1) with former cigarette smokers by number of cigarettes smoked per day and years since cessation of smoking (Hrubec and McLaughlin 1997).**

Duration of Cessation (years)	Former Smoker by Number of Cigarettes				
	1-9	10-20	21-39	40+	Total
<5	7.6	12.5	20.6	26.9	16.1
5-9	3.6	5.1	11.5	13.6	7.8
10-19	2.2	4.3	6.8	7.8	5.1
20-29	1.7	3.3	3.4	5.9	3.3
30-39	0.5	2.1	2.8	4.5	2.0
≥40	1.1	1.6	1.8	2.3	1.5
Total	1.4	3.3	5.0	6.9	3.6

**Table I-2. Risk of death from coronary heart disease compared with lifetime non smokers (Hrubec and McLaughlin 1997).**

Years of Cessation	Men
<5	1.7
5-9	1.5
10-19	1.4
20-29	1.2
30-39	1.1

This study reports relative lung cancer risk at various time intervals following cessation of smoking compared with non-smokers and does not make a direct comparison with present smokers. The study combines a very large cohort with a followup of sufficient length that about 2/3 of the cohort was deceased at the time of the study. The length of the followup is of particular importance in smoking studies because lung cancer deaths are relatively uncommon. The number of lung cancer deaths among nearly 200,000 deceased members of the cohort is large enough to allow an accurate assessment of relative risks for lung cancer. The use of veterans also decreased potential bias since veterans can be expected to be a more uniform cohort in terms of health status and lifestyle than the general population. This study was selected as a source of smoking cessation data for statistical modeling because of the large number of lung cancer and coronary heart disease deaths and the uniformity of the cohort.

## *2. Burns et al. (1997)*

A second very large study was reported at the same time by Burns *et al.* (1997). 1,078,894 volunteer men and women were enrolled in the study. Most were enrolled during late 1959. Relative risks for lung cancer mortality compared with present smokers were calculated for both men and women who had previously smoked either 1-9, 10-19, 20, 21-39, 40+ cigarettes with cessation durations of 2-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, and 35-39 years. For all white male former cigarette smokers, the RRs were 13.12, 8.44, 4.61, 2.89, 2.04, 1.19, 1.84, and 3.18. Similar data were reported for white females, although the data sets were less complete because of inadequate number in some groups.

This study has some advantages compared with the U.S. veterans study. The number of individuals enrolled is greater and females were included in the study. Relative risks for continuing smokers were also reported. Although greater numbers were enrolled, fewer of the subjects were deceased because of a somewhat shorter time period from initiation of the study. Death data were reported for 117 thousand males and 88 thousand females. Moreover, because of a smaller number of deceased females, combined with smaller numbers of lung cancer related deaths, the data sets for females are less complete with greater levels of uncertainty. Finally, the

95% upper and lower confidence limits of the RRs are reported in the veterans study, but not in the volunteer study. For these reasons, the Burns *et al.* (1997) data were not selected for statistical modeling. A summary of results are shown in Tables I-3, I-4, and I-5. The lung cancer and coronary heart disease mortality reduction for white males shown in Tables I-3 and I-5 approximately parallels that of the veteran study.

**Table I-3. Lung cancer relative risks for white male former smokers by duration of cessation and level of cigarette consumption—comparison never smoker group weighted former smoker person-years of observation for each (age x duration x cigarettes per day) cell (Burns *et al.*, 1997).**

Duration of Cessation (years)	Former Smoker by Number of Cigarettes					
	1-9	10-19	20	21-39	≥40	Total
2-4	2.83	7.96	11.68	14.30	27.88	13.12
5-9	1.68	3.50	10.49	9.18	12.36	8.44
10-14	1.22	2.91	5.03	4.85	7.77	4.61
15-19		2.04	2.22	4.88	3.74	2.89
20-24		0.96	1.86	2.04	3.99	2.04
25-29	0.58	2.16	1.12		0.89	1.19
30-34	1.38	1.68	1.55	4.13		1.84
35-39	1.89		4.10	3.69		3.18

**Table I-4. Mortality rates for white female former smokers by duration of cessation and level of cigarette consumption— comparison never-smoker group weighted to match former smoker person-years of observation for each (age x duration x cigarettes per day) cell (Burns *et al.*, 1997).**

Duration of Cessation (years)	Former Smoker by Number of Cigarettes					
	1-9	10-19	20	21-39	≥40	Total
2-4	2.13		4.31			2.85
5-9	1.89	0.95				1.51

10-14	0.45	0.61	0.76			0.58
15-19		3.06	0.98	16.99		3.19
20-24	2.38	2.42	1.66	10.90		2.52
25-29	1.81	3.65				2.61
30-34						
35-39						

**Table I-5. Risk of death from coronary heart disease compared with lifetime nonsmokers (Burns *et al.*, 1997).**

<b>Years of cessation</b>	<b>Men</b>	<b>Women</b>
2-4	2.23	2.66
5-9	1.53	1.64
10-14	0.98	1.37
15-19	0.84	1.13
20-24	0.88	0.97
25-29	0.96	0.96
30-34	0.63	0.93
35-39	0.63	0.55

### *3. Doll and Peto (1976)*

A study by Doll and Peto (1976) included 34,440 male British doctors enrolled in 1951. After 20 years 10,072 deaths were reported. The cause of death was recorded for lung and other cancers, respiratory diseases, cardiac and vascular diseases, a variety of other diseases, and violence. Mortality in ex-cigarette smokers was compared with continuing smokers after < 5, 5-9, 10-14, and 15 years since cessation of smoking. Mortality in ex-smokers was also compared with mortality in lifetime non-smokers after 0, <5, 5-9, 10-14, and 15 years since cessation of smoking.

This is a useful supporting study since comparisons are made with both continuing smokers as well as lifetime non-smokers. Uncertainty in the values, however, is greater than in the above two studies because of the smaller number of individuals enrolled and smaller number deceased. Only 15 deaths from lung cancer were reported among those that had stopped smoking for less than 5 years, 12 deaths in the 5-9 year groups, 9 deaths in the 10-14 year group and 7 in the 15 year group. The followup was also of shorter duration than in the previous two studies and the cohort was composed of a very stratified social economic group. Results are summarized in Table I-6 and I-7.

**Table I-6. Cancer mortality in ex-cigarette smokers by number of years they had stopped smoking compared with mortality in either continuing smokers, or lifelong non smokers (Doll and Peto, 1976).**

Duration of cessation (years)	Relative Risk	
	Compared with non smokers	Compared with continuing smokers
0	15.8	
<5	16.0*	1.02
5-9	5.9	0.35
10-14	5.3	0.28
15	2.0	0.11

\*When 5 men were excluded who stopped smoking after they developed lung cancer the ratio was reduced to 10.7

**Table I-7. Risk of death from ischemic heart disease compared with lifetime nonsmokers (Doll and Peto, 1976).**

	Age in Years		
Years of cessation	30-54	55-64	>65
0	3.5	1.7	1.3
<5	1.9	1.9	1.0
5-9	1.3	1.4	1.3
10-14	1.4	1.7	1.2
15	1.3	1.3	1.1

#### 4. *Lubin et al. (1984)*

Two major case-control studies of smoking cessation have been published. A study of lung cancer hospital patients in western Europe includes a study population of 7,181 cases and 11,006 controls (Lubin *et al.*, 1984). Patients included 6631 men and 551 women. Controls included 10,439 men and 567 women. Only patients with histologically confirmed lung cancer were included. Controls matched for age at diagnosis, sex, center, and, if possible, category of hospital accommodation, were selected from other hospital patients in whom diseases not related to tobacco had been diagnosed. The relative risk of lung cancer mortality, compared with continuing smokers was reported for both men and women 1-4, 5-9, 10-14, 15-19, 20-24, and  $\geq 25$  years after cessation of smoking. The decrease in relative risk after cessation of smoking for 1-4, 5-9 and  $\geq 10$  years was also reported for durations of smoking habit ranging from 1-19, 20-39, 40-49, and  $\geq 50$  years and for 1-9, 10-19, 20-29, and  $\geq 30$  cigarettes per day.

Since the number of cases was quite large, uncertainty regarding relative estimates is likely to be quite small. Confidence intervals for the relative risk estimates, however, were not reported. The results suggest that relative risk compared with non-smokers declines more rapidly with duration of cessation of smoking as number of cigarettes per day formerly smoked increases. On the other hand, the decrease in relative risk with duration of cessation is slower as the number of years of smoking increased. Lung cancer mortality risks are related to those of current smokers, so results cannot be directly compared with the previous studies in which risks of former smokers are compared with those of lifetime nonsmokers. Results are summarized in Table I-8.

**Table I-8. Relative risk of developing lung cancer by number of years since stopped smoking, controlling for several factors. All risks adjusted for duration of use in years (Lubin *et al.*, 1984).**

	<b>Relative risk compared with current smokers</b>	
<b>Duration of Cessation (years)</b>	<b>Men</b>	<b>Women</b>
0	1.00	1.00
1-4	1.07	0.94
5-9	0.71	0.68
10-14	0.56	0.36
15-19	0.43	0.49
20-24	0.43	0.47
≥25	0.29	0.27

5. *Peto et al (2000)*

Peto *et al.* (2000) reported results from a case-control study conducted in 1990 in southwest England. Potential cases were patients younger than 75 who were referred with suspected lung cancer to hospitals in Devon and Cornwall. Controls living in the same area were selected from hospital admissions for diseases considered not related to smoking. Information was obtained about the smoking habits of 667 men and 315 women with a confirmed diagnosis of lung cancer and of 2,108 male and 1,077 female controls. Lung cancer risk of former smokers was compared with current smokers after less than 10, 10-19, 20-29, and > 30 years since cessation of smoking. Lung cancer risk of former smokers could also be compared with those of lifetime non-smokers, based upon the ratios of risk for current smokers in the present versus lifetime nonsmokers in the U.S.

This study is well designed with elimination of most potential confounding factors by careful matching of cases and controls for a variety of variables such as age, social economic status, race, lifestyle, etc. The number of cases, while adequate is smaller than in the previous study. Moreover, the rate of decline of risk during the first 10 years following cessation of smoking cannot be modeled as accurately as possible with the previous study, since results were reported for only one period during the first ten years post smoking cessation. Confidence intervals for the risk ratios were also not reported. Thus, while this is an acceptable case-control study for modeling the decrease in lung cancer risk following cessation of smoking, the Lubin *et*

*al.* (1984) study is considered to be superior because of a larger number of cases and shorter time intervals following smoking cessation. Results are summarized in Table I-9.

**Table I-9. Comparisons of risk of lung cancer between all current smokers, all former smokers, and lifelong non-smokers in 1990 study. (Peto *et al.*, 2000).**

	Men		Women	
Duration of cessation (years)	Risk ratio <sup>a</sup> Nonsmoker	Risk ratio <sup>b</sup> Smoker	Risk ratio <sup>a</sup> Nonsmoker	Risk ratio <sup>b</sup> Smoker
0		1.00		1.00
<10	14.4	0.66	14.6	0.69
10-19	10.0	0.44	4.5	0.21
20-29	4.7	0.20	1.9	0.05
>30	2.2	0.10	1.9	0.05
Non smoker	1.0	0.03	1.0	0.05

<sup>a</sup>Relative risk of cancer mortality of former smokers compared with lifelong non-smokers

<sup>b</sup>Relative risk of cancer mortality of former smokers compared with continuing smokers.

#### 6. *La Croix et al. (1991)*

*La Croix et al.* (1991) prospectively examined the relation of cigarette-smoking habits with mortality from all causes, cardiovascular causes and cancer among 7,178 persons 65 years of age or older without a history of myocardial infarction, stroke, or cancer who lived in either East Boston, Massachusetts; Iowa and Washington counties, Iowa; and New Haven, Connecticut. Approximately 11,000 participants were followed for 5 years. Cardiovascular and cancer mortality were recorded for never smokers and for former smokers who had stopped smoking for ≤5, 6-10, 11-20 and >20 years. Relative risks for cancer mortality with 95% confidence intervals compared with never smokers were reported. The usefulness of this study is limited because lung cancer was not specifically reported. Results are summarized in Tables I-10 and I-11.

**Table I-10. Relation of cigarette smoking with the risk mortality from all cancers among former smokers in comparison with lifetime nonsmokers (LaCroix *et al.*, 1991).**

Duration of Cessation (years)	Mortality from cancer (Relative Risk)	
	Men	Women
≤5	1.1	1.4
6-10	2.1	0.7
11-20	2.4	1.2
>20	0.8	1.2

**Table I-11. Risk of death from cardiovascular mortality compared with lifetime nonsmokers (LaCroix *et al.*, 1991).**

Years of cessation	Men	Women
≤5	1.1	1.0
6-10	0.9	1.0
11-20	1.1	0.5
>20	1.0	0.8

### **Conclusions:**

Results of the five studies in which lung cancer mortality was reported are summarized in Table I-12. Results agreed quite well when comparisons were made between former smokers and either present smokers or lifetime non smokers. The only directly comparable time periods for the three prospective studies were less than 5 years and 5-9 years. The lung cancer mortality risk during the 5-9 year cessation of smoking period was 48%, 64%, and 55% of that reported during the less than 5 year period for the Hrubec and McLaughlin (1997), Burns *et al.* (1997) males and Doll and Peto (1976), respectively. In the Lubin *et al.* (1984) case-control study, the risk at 5-9 years of cessation was decreased to 66% of that of the 1-4 year period. Differences may well be a reflection of the differing ages of the cohorts or cases, differing duration of smoking as well as number of cigarettes smoked.

**Table I-12. Relative risk of lung cancer mortality following cessation of smoking; summary of 5 studies.**

	Relative risk compared with lifetime nonsmokers			
Duration of smoking cessation (years)	Hrubec and McLaughlin (1997)	Burns <i>et al.</i> (1997)	Doll and Peto (1976)	Peto <i>et al.</i> (2000)
0			15.8	
<5	16.1	13.1	16.0	
<10				14.4
5-9	5.9	8.4	5.9	
10-14		4.6	5.3	
10-19	5.1			10.0
15-19		2.9		
	Relative risk compared with present smokers			
Duration of smoking cessation (years)	Lubin et al (1984) Men	Lubin et al (1984) Women	Peto et al (2000)	
0	1.00	1.00	1.00	
1-4	1.07	0.94		
<10			0.66	
5-9	0.71	0.68		
10-14	0.56	0.36		
10-19			0.44	
15-19	0.43	0.49		
20-24	0.43	0.47		
20-29			0.20	
>25	0.29	0.27		
>30			0.10	

## I.2. Studies of Coronary Heart Disease

### 1. *McElduff et al., 1998*

A case-control study of heart disease occurring in men and women aged 35-64 living in Newcastle, Australia and Auckland New, Zealand has been reported (McElduff *et al.*, 1998). Cases were 5,572 people identified in population registers of coronary events and 6,268 matched controls. The data included both fatal and nonfatal coronary events. The data suggest that risk decreases little, if any, the first year of cessation of smoking, then declines to non smoker levels after 12 years. The results are shown in Table IV-13.

**Table I-13. Reduction of coronary risk attributable to smoking cessation.**

	Newcastle		Auckland	
Duration of cessation	Men	Women	Men	Women
Never smoker	1.00	1.00	1.00	1.00
Current smoker	3.6	4.7	3.9	6.2
1-5 months	14.1	7.4	4.7	2.7
6-12 months	4.4	3.2	3.8	3.7
1-3 years	1.9	1.9	2.3	2.7
4-6 years	1.5	1.3	1.8	0.9
7-9 years	1.6	1.2	1.1	1.9
10-12 years	1.7	1.7	1.0	2.3
> 12 years	1.0	0.9	1.0	0.8

The relationship of cardiac mortality to smoking cessation has been reported by Omen *et al.* (1990). The authors investigated the excess mortality risks of former smokers in a cohort of 21,112 men and women evaluated with coronary angiography and included in the Coronary Artery Surgery Registry. The results are listed in Table I-14.

**Table I-14. Risk of cardiac mortality compared with lifetime nonsmokers**

<b>Duration of cessation</b>	<b>Men</b>	<b>Women</b>
Current smoker	1.45	1.74
< 1 year	1.04	1.34
2-9 years	1.08	1.28
10-19 years	1.18	1.11
> 19 years	1.01	0.85

2. *Rosenberg et al. (1985)*

A case-control study of 1,873 men with first episodes of myocardial infarction and 2,775 controls has been reported (Rosenberg *et al.* 1985). This is thus not a mortality study, but one that measures the incidence of a cardiac event. Relative risks were taken from a graph. The results are shown in Table I-15.

**Table I-15. Risk of a cardiac event versus time following smoking cessation.**

<b>Duration of cessation</b>	<b>Relative risk</b>
12-23 months	2.9
24-35 months	2.0
3-4 years	1.1
5-9 years	1.3
10-14 years	1.0
15-19 years	1.3
≥20 years	0.8

### **I.3. Statistical Modeling**

#### **I.3.1. Lung Cancer**

The derivation of a model based on smoking cessation that can also be used to characterize cessation lag for As and other carcinogenic drinking water contaminants involved two primary steps:

1. Model fitting and associated statistical testing using the smoking cessation data;
2. Application of the smoking cessation-based model to other exposure reduction events.

### *Model Fitting Using the Smoking Cessation Data*

The study by Hrubec and McLaughlin (1997) described above was selected for statistical modeling. This study presented data on tobacco use and mortality in a 26-year follow-up study of almost 300,000 U.S. male veterans. The modeling of changes in relative risk of lung cancer following cessation of smoking is based upon the data summarized above in Table 1 and includes consideration of both the duration of cessation (time since stopping smoking) and the daily number of cigarettes smoked prior to cessation.

These data were used to develop a cessation lag model having the following general form:

$$RR_{ij} = B_i \cdot (Y_j)^{-K_i} \quad (1)$$

In this model,  $RR_{ij}$  refers to the relative risk for an individual in the  $i$ th category of daily cigarettes smoked prior to cessation following  $Y_j$  years of cessation. Note that risk is relative to that of never-smokers. The model was fit using the mid-point of each 5-year post-cessation time interval examined by Hrubec and McLaughlin. Note also that the model is considered valid only for cessation periods of one year or more ( $j \geq 1$ ). Extrapolation of the model below one year is questionable based on the available data. Furthermore, extrapolation below one year seems inappropriate because of the unlikelihood that cessation of a risk agent such as As ingestion or smoking would result in a benefit to an individual with a disease so advanced that he/she would otherwise succumb to that disease in a year or less. We therefore assume that there is no risk reduction in the first year after cessation of smoking.

The general model shown in (1) can be converted to a linear form by taking the logarithm of both sides:

$$\text{Log}(RR_{ij}) = \text{log}(B_i) - K_i(Y_j) \quad (2)$$

A random effects model was used to examine the influence of pre-cessation smoking amount on the model parameters. A random effects model was used in this analysis because the pre-cessation smoking amount classification used by Hrubec and McLaughlin is only one of many possible classifications. Equation (2) can be re-stated to introduce random effects terms as:

$$\text{log}(RR_{ij}) = (\alpha + a_i) + (\beta + b_i) \text{log}(Y_j) + \varepsilon_{ij} \quad (3)$$

In this expression of the model,  $\alpha$  and  $\beta$  are the population average intercept and the population average slope terms, respectively. The  $a_i$  and  $b_i$  terms are the random effects in intercept and slope associated with the  $i$ th smoking level category, and  $\varepsilon_{ij}$  is the within cell error term. It is assumed that random effect terms are independent and identically distributed with a normal distribution of 0 mean and constant variance.

A key objective of this model evaluation step was to determine whether and how the daily number of cigarettes smoked before cessation affected the model parameters, that is, whether there are statistically significant differences in the intercept and slope terms for each dose group as reflected by statistically significant differences in the  $a_i$ 's and in the  $b_i$ 's.

To test for differences in the intercept and slopes using the random effects model, two alternative models were considered:

$$\log(\text{RR}_{ij}) = (\alpha + a_i) + \beta \log(Y_j) + \varepsilon_{ij} \quad (4)$$

$$\log(\text{RR}_{ij}) = \alpha + (\beta + b_i) \log(Y_j) + \varepsilon_{ij} \quad (5)$$

When the random effect term  $b_i$  is removed, the model in equation (4) is fitted and compared with the full model in equation (3). The comparison indicates model (3) and model (4) are not different from each other based on a Chi-square test, i.e., the term  $b_i$  is not significantly different from 0 ( $p = 0.9973$ ), which supports the conclusion that the slope parameter is independent of pre-cessation dose group.

However, when the term  $a_i$  is removed from equation (5), the resulting model is significantly different from the full model equation (2) ( $p = 0.0001$ ). This indicates that the intercept terms are dependent upon the pre-cessation dose.

Based on these results, we select equation (4) as our model of log-relative risk following cessation lag. Transformed back to the relative risk scale, the model is

$$\text{RR}_{ij} = B_i \cdot (Y_j)^{-K} \quad (6)$$

where there are different starting relative risks  $B_i$  in each exposure group, but a common rate  $K$  of decrease. The resulting parameter estimates, obtained by linear regression analysis of model (4), are:

<u>Coefficient</u>	<u>Value</u>	<u>Std. Error</u>
Log( $B_1$ )	2.772	0.320
Log( $B_2$ )	3.416	0.320
Log( $B_3$ )	3.772	0.320
Log( $B_4$ )	4.070	0.320
K	-0.77	0.052

The general model shown in (1) above can therefore be re-stated as:

$$RR_{ij} = B_i \cdot (Y_j)^{-0.77} \quad (7)$$

The different intercepts result implies that an individual's relative risk of lung cancer is different at the point when cessation begins as a function of the daily number of cigarettes smoked up to that point in time. Further, as indicated by the intercept values noted above, the relative risk is greater for the higher dose groups than the lower dose groups, as would be expected.

The finding that the slope parameter is not different across the different pre-cessation dose groups indicates that the rate at which relative risk decreases following smoking cessation is similar regardless of pre-cessation dose level. It will take longer for individual's in the higher dose groups than in the lower dose groups to approach the relative risk of 1 (i.e., the never smokers) because the former have a higher relative risk at the point when cessation occurs than do the latter. However, the *rate* of decline in relative risk from one year to the next appears to be the same for all dose groups.

The discussion of the application of the smoking cessation model to estimate the rate of risk reduction for other environmental carcinogens, such as As, follows.

#### *Application of the smoking cessation-based model to other exposure reduction events*

For the application of the smoking cessation model to other exposure reduction situations, (such as implementing an As MCL), the focus of interest is on the proportional changes in relative risk over time following the initiation of exposure reduction. If the relative risks are known for individuals at both the high (pre-regulation) and low (post-regulation) exposure conditions, then the cessation lag model reflecting the proportional change in relative risk over time can be used to estimate at any point in time the percent of the maximum change in risk that has occurred as individuals are in transition from the higher to the lower risk level.

Keeping in mind that the percent of the maximum change in risk that occurs over time is 100%, the smoking cessation model can be used to estimate the percent of changes in relative risk as follows. If we call  $Z_j$  the percent of the maximum risk reduction that occurs after  $j$  years of smoking cessation, then we can compute  $Z_j$  in any year for any starting dose group (i) from:

$$Z_j = 100 \cdot ([B_i \cdot (Y_1)^{-0.77}] - [B_i \cdot (Y_j)^{-0.77}]) / [B_i \cdot (Y_1)^{-0.77}] \quad (8)$$

Noting that  $Y_1 = 1$  and that the  $B_i$  terms cancel out, Equation (8) can be simplified as

$$Z_j = 100 \cdot [1 - (Y_j)^{-0.77}] \quad (9)$$

Using this equation, the percent of the maximum risk reduction that has been achieved after the change in exposure can be computed for any year  $j$ . Examples are:

<u>Year after Exposure Reduction</u>	<u>% of Maximum Risk Reduction</u>
1	0.0%
2	41.4%
3	57.1%
4	65.6%
5	71.0%
10	83.0%
20	90.0%

It should be pointed out again that the relative risk reductions derived from Hrubec and McLaughlin (1997) apply to a complete cessation of smoking, that is, a reduction to zero exposure. In the case of a revised As MCL, exposure will not drop to zero. It will drop to the new MCL, which is greater than zero. In this case, we apply the estimated % of maximum risk reductions to the difference in risk between the old and new exposure levels. For example, if As exposure drops from 50 ppb to 10 ppb, then after two years the risk is estimated to decrease by 41.4% (as shown above) of the excess risk of 50 ppb compared to 10 ppb. In this way, over time the new risk level approaches the risk at 10 ppb.

The reduction in risk following exposure reduction can also be expressed mathematically as follows. Let  $h(t,c)$  be the risk at age  $t$  and As concentration  $c$ , in the case where  $c$  is assumed to be constant over time. Now suppose that at age  $t_0$ , exposure is reduced from a high level,  $c_H$ , to a new low level,  $c_L$ . Then at  $y$  years following the exposure reduction, the new risk is

$$h^*(t_0+y) = h(t_0+y, c_L) + w(y) \cdot (h(t_0+y, c_H) - h(t_0+y, c_L)) \quad (10)$$

where  $w(y)$  is the weight function, decreasing from 1 to 0 with increasing time  $y$ , that describes the decrease in excess risk over time. The weight function is determined from equation (6) : rescaling RR to a maximum of 1 after 1 year of exposure reduction, we have  $w(y) = y^{0.77}$ . As mentioned above, this weight function is valid only for  $y > 1$  years of exposure reduction; for the first year after exposure reduction, no risk reduction is assumed to occur, so  $w(y)=1$  for  $0 \leq y \leq 1$ . By equation (9), the risk following exposure reduction eventually approaches the risk corresponding to the new, lower exposure level.

One uncertainty in this modeling is that the data in Hrubec and McLaughlin do not include the number of years of smoking before cessation (only the number of cigarettes smoked daily before cessation). We therefore cannot use the data from Hrubec and McLaughlin to model the effect of duration of exposure on cessation lag. Instead we assume that cessation lag is independent of duration of exposure. There is some support for this assumption in our finding, above, that the cessation lag is independent of the level of exposure (number of cigarettes smoked

per day) before quitting. For a constant duration of exposure, a higher rate of smoking implies higher lifetime exposure, yet there is no evidence that this affects the length of cessation lag. This finding tends to support the assumption that increased duration of exposure, though it clearly increases overall risk, does not affect the rate at which risk decays after cessation.

Once the risks following exposure reductions have been estimated as above, a larger model is required in order to translate the risk reductions into numbers of cases avoided and corresponding benefits over time. Such a benefits model must take into account not only risk but existing occurrence distributions, demographic information such as age and sex distributions, drinking water consumption, regional differences, the new MCL, treatment effectiveness, and valuation of cases avoided. Such a calculation is beyond the scope of this document. A proposed approach is described in US EPA (2002) and is currently undergoing external peer review.

### **I.3.2. Coronary Heart Disease**

Hrubec and McLaughlin presented data on tobacco use and mortality in a 26-year follow-up study of almost 300,000 U.S. male veterans. From Table 5 of that report, the RRs for coronary heart disease (CHD) were listed as 1.7, 1.5, 1.4, 1.2 and 1.1 following cessation of smoking for <5, 5-10, 10-20, 20-30, and 30-40 years, respectively.

The RR declined as a first-order function, i.e., at a constant rate (K), over the number of years since smoking (t):

$$RR = RR_0 \cdot e^{-Kt}, \quad (11)$$

where  $RR_0$  is the RR at the time smoking was ceased. Using the midpoint of the time for each cessation group, the estimates of the model parameters with  $\pm$  standard errors are  $RR_0 = 1.70 \pm 0.06$  and  $K = 0.0130 \pm 0.0009$ . The relatively small standard errors indicate a good fit of the model:

$$RR = 1.70 \cdot e^{-0.0130 \cdot t}. \quad (12)$$

A minimum RR of 1.0 for never smokers is given by Hrubec and McLaughlin. From these data the maximum achievable reduction in the RR is  $(1.70-1.00) = 0.70$ . After one year of smoking cessation, from equation (9) the RR is estimated to be 1.678. Thus,  $[(1.70-1.678)/0.70] \times 100\% = 3.14\%$  of the maximum achievable reduction in the RR is estimated to occur for the first year of smoking cessation. After two years, the estimated RR is 1.6564. Hence,  $[(1.678-1.6564)/0.70] \times 100\% = 3.09\%$  of the maximum achievable reduction occurs during the second year. For the third year, the RR is estimated to be 1.635, and the reduction to be  $[(1.6564-1.635)/0.70] \times 100\% = 3.06\%$  of the maximum achievable risk.

If the reduction of ischemic heart disease (ISHD) mortality rates after the reduction of As

in drinking water follows the same pattern of reduction as the SMR after cessation of cigarette smoking, then the reduction in the number of cases of ISHD mortality can be estimated for each year following implementation of a new As MCL. For example, for those individuals in the population currently exposed to 45 ppb and subsequently to a new MCL below 30 ppb (the As RfD for ISHD), from the dose-response equation for ISHD the maximum achievable reduction in the lifetime risk of ISHD mortality is estimated to be  $(0.0000298) \times (45) = 0.00134$ . The value of 30 ppb is a floor below which no ISHD effect occurs and no further benefit accrues. For reasons stated above, it is assumed that during the first year of exposure reduction there is no risk reduction. The estimated risk reduction during the second year (3.09%) is estimated to be  $(0.0309 \times 0.00134) = 0.0000414$ , during the third year (3.06%) is estimated to be  $(0.0306 \times 0.00134) = 0.0000410$ , etc. This process would need to be repeated for those individuals exposed to each current concentration at or above 30 ppb, and then all such group estimates summed to obtain estimates for the whole population.

#### **I.4. Conclusions**

EPA has concluded the following with respect to issues pertaining to cessation lag:

1. There are not sufficient data available for ingested As or other ingested toxicants with which to quantitatively predict the cessation-lags, as defined by SAB (U.S. EPA, 2001), that are applicable to the reductions in risk of cancer and noncancer disease endpoints resulting from a reduction in exposure to As in drinking water.
2. The most useable data for development of statistical models to predict cessation-lag for ingested As are those that define risk reduction associated with smoking cessation for the following reasons:
  - The smoking cessation data are extensive, consisting of numerous studies for both cancer and noncancer endpoints.
  - The smoking cessation studies report lung cancer and coronary heart disease, which are also endpoints for ingested As.
  - The smoking cessation cohorts are large, which reduces statistical uncertainty.
3. The study by Hrubec and McLaughlin (1997) provides the most appropriate data on which to base statistical models of cancer risk reduction resulting from smoking cessation. This study was selected because of its long follow-up period, which results in high mortality among the subjects, and the uniformity of the cohort.
4. Statistical models for lung cancer can serve to predict cessation-lag for all ingested As cancers because of the presumed common modes of action for these cancers. Likewise, statistical models for coronary heart disease can be applied to ingested As incidence or mortality calculations for all of the primary internal As noncancer endpoints because of a common mode of action for these effects.
5. The models described in this report can be applied to calculated incidence or mortality values in order to estimate the cessation-lags in risk reduction resulting from a reduction in exposure to As in drinking water.

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